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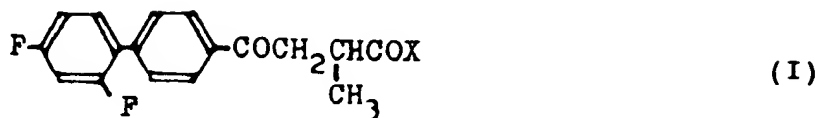
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W-8000 München 90(DE)**(54) **Derivatives of 4-(2,4-difluoro-biphenyl)-2-methyl-4-oxo-butanoic acid.**

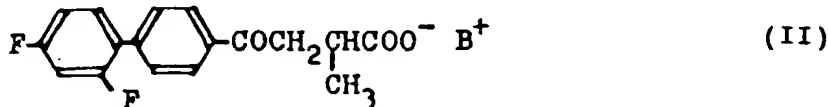
(57) This invention relates to substances represented by Formula (I), wherein X stands for either OR in which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(CH_2)_nNR'_2$ group wherein n is 2 or 3 while R' is a methyl or ethyl group; eventually X may represent morpholinyl. Also considered are salts of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by Formula (II) wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation. Said substances are characterized by anti-inflammatory properties comparable to (and greater than) the initial acid while simultaneously said modifications of their physico-chemical properties broaden the possibilities of their therapeutic application.

EP 0 465 879 A1

This invention relates to 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid having the following general formula (I)



wherein X stands for OR in which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(\text{CH}_2)_n\text{NR}'_2$ group wherein n is 2 or 3 while R' is a methyl or an ethyl group; eventually X may represent morpholinyl. This invention further relates to salts of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by the general formula (II)



wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation.

Recently a significant prolonged anti-inflammatory effect of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid has been recognized (CS-AO 243 570). An analogous anti-inflammatory effect was found in several functional derivatives and salts of said acid. Some of the substances of general formulae (I) and (II) are characterized by physico-chemical properties, incl. increased solubility in water, which broaden their therapeutic application without any noticeable decrease of their anti-inflammatory effect. Changes in lipophilicity eventually differing biotransformation of esters and amides in comparison with the free acid may influence the pharmacokinetic behaviour of these derivatives. Results of the pharmacological evaluation of substances (I) and (II) are summarized in Table (I). Simultaneously, these substances are characterized by low toxicity, incl. a low ulcerogenic effect. They may be used for the preparation of therapeutic compositions which may contain the effective substance in combination with pharmacologically acceptable ingredients, liquid or solid, which are usually used in the manufacture of application forms.

Example 1

Ethoxycarbonylmethylamide 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

5.0 g of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is dissolved in a mixture of 35 ml dimethylformamide and 150 ml dichloromethane. 2.1 g N-ethylpiperidine is added to the solution and 2.05 g ethylchloroformate is added after cooling to -15°C . After stirring for 30 minutes at -15°C the mixture is cooled to -30°C and 1.7 g glycineethyl ester in 35 ml dichloromethane is added. The mixture is left at room temperature to warm up to 20°C and at this temperature it is stirred for 2 hours. Thereafter, the mixture is consecutively washed 3 times in a separation funnel in 100 ml 5% NaHCO_3 , once in 100 ml H_2O , 3 times in 100 ml 1 N HCl, and once again in 100 ml H_2O .

Water is adsorbed by Na_2SO_4 from the organic part which is then dried by evaporation and the crystalline residue is purified by crystallization in acetone. Yield: 4.3 g (67.2 % theor.) of the ethoxycarbonylmethylamide (melting point $95-96^\circ\text{C}$);

for $\text{C}_{21}\text{H}_{21}\text{NF}_2\text{O}_4$ (389.4)

calculated: 64.77 % C, 5.44 % H, 3.58 % N, 9.76 % F;
found: 64.84 % C, 5.35 % H, 3.34 % N, 9.66 % F;
 $^1\text{H-NMR}$ (C^2HCl_3): δ (2-CH_3) = 1.30 d, J = 7.0 Hz;
 δ (NH) = 6.36 bt;
 δ (aromat. ortho-CH) = 8.05 d, J = 8.5 Hz.

Similarly were prepared:

Ethylamide of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with a 72.8 % recovery (melting point 128°C , crystallized in acetone);

for $\text{C}_{19}\text{H}_{19}\text{NF}_2\text{O}_2$ (331.4)

calculated: 64.77 % C, 5.44 % H, 3.58 % N, 9.76 % F;
 found: 64.84 % C, 5.35 % H, 3.34 % N, 9.66 % F;
¹H-NMR (C²HCl₃): δ (2-CH₃) = 1.30 d, J = 7.0 Hz;
 δ (NH) = 6.36 bt;
 δ (aromat. ortho-CH) = 8.05 d, J = 8.5 Hz.

Morpholide of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with a 65.8 % recovery (melting point 95-97 °C, crystallized in acetone) (n-hexane, 4:1);
 for C₂₁H₂₁NF₂O₃ (373.4)

calculated: 67.55 % C, 5.69 % H, 3.75 % N, 10.18 % F;
 found: 67.36 % C, 5.81 % H, 3.66 % N, 10.29 % F;
¹H-NMR (C²HCl₃): δ (2-CH₃) = 1.22 d, J = 7.0 Hz;
 δ (CH₂ morpholine) = 3.68 bs;
 δ (aromat. ortho-CH) = 8.07 d, J = 8.5 Hz.

Example 2

Ethylester of 4-(2,4-difluorobiphenyl)-4-oxobutanoic acid

1.2 ml thionylchloride is added to 20 ml ethanol, cooled to - 15 °C and then, 4.0 g 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is added in four portions while the temperature is kept at -10 °C by cooling. At this temperature it is stirred for 30 minutes; then, instead of cooling the mixture is heated to 40-45 °C for two hours. Ethanol is vacuum evaporated and the residue is dried by double vacuum distillation with 20 ml benzene. After crystallisation in acetone the crude product gives 3.0 g (68.5 % theor.) of ethylester (melting point 67-68 °C)

for C₁₉H₁₈F₂O₃ (332.4)

calculated: 68.66 % C, 5.46 % H, 11.43 % F;
 found: 68.41 % C, 5.41 % H, 11.37 % F;
¹H-NMR (C²HCl₃): δ (2-CH₃) = 1.30 d, J = 7.0 Hz;
 δ (CH₂) ester = 4.16 q, J = 7.0 Hz;
 δ (arom. ortho-CH) = 8.06, J = 8.5 Hz;

Similarly were prepared:

Isobutylester of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with a 90.5 % recovery (melting point 50-52 °C)

for C₂₁H₂₂F₂O₃ (360.4)

calculated: 69.98 % C, 6.15 % H, 10.54 % F;
 found: 69.78 % C, 6.16 % H, 10.28 % F;
¹H-NMR (C²HCl₃): δ (CH₃ isobutyl) = 0.92 d, J = 7.0 Hz;
 δ (2-CH₃) = 1.30 d, J = 7.0 Hz;
 δ (aromat. ortho-CH) = 8.08 d, J = 8.5 Hz.

Example 3

n-Butylamide of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

0.2 ml dimethylformamide is added to a suspension of 6.0 g 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid in 40 ml benzene and then, within 10 minutes 20 ml solution of thionylchloride in 20 ml benzene is added. Then, the mixture is heated to boiling (the suspension becomes a solution) and is kept at this temperature while stirring for 45 minutes. The reaction mixture is vacuum condensed and the residue redissolved in 50 ml benzene and condensed until dry. The thus obtained chloride of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is mixed with 50 ml benzene and the solution is filtered with activated carbon. The clear filtrate is slowly added to a solution of 2.90 g of n-butylamine in 20 ml benzene cooled to 5 °C. The mixture is then kept for 1 hour at 5 °C and for 2 hours at 20 °C. The opaque solution is washed consecutively in 100 ml 1N HCl, 100 ml H₂O, twice in 100 ml 5 % NaHCO₃ and again in 100 ml H₂O. After drying with magnesiumsulphate the benzene is distilled off in vacuum and the crude product is crystallized in acetone. n-butylamide of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid (melting point 114-115 °C) and recovery of 72.5 % is obtained.

for C₂₁H₂₃F₂O₃ (359.4)

calculated: 70.18 % C, 6.45 % H, 3.90 % N, 10.57 % F;

found: 70.40 % C, 6.60 % H, 3.89 % N, 10.44 % F;
¹H-NMR (C²HCl₃): δ (2-CH₃) 0 1.25 d, J = 7.0 Hz;
 δ (NH) = 5.86 bt;
 δ (aromat. ortho-CH) = 8.06 d, j = 8.5 Hz.

5

Example 4

Cyclohexylammonium salt of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

10 4.0 g of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is dissolved in 40 ml acetone and to the clear solution a solution of 1.32 g cyclohexylamine in 20 ml ether is added under constant stirring and cooling at 20 ° C. Immediately a sediment begins to precipitate and ends after 2 hours of cooling at 0 ° C. The precipitate is removed and thoroughly washed in cooled acetone. 4.6 g (86.1 % theoret.) of the sought product (melting point 139-140 ° C) is obtained.

15 for C₂₃H₂₇F₂O₃ (403.5)

calculated: 68.47 % C, 6.75 % H, 3.47 % N, 9.42 % F;

found: 68.18 % C, 6.74 % H, 3.42 % N, 9.25 % F.

Example 5

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Potassium salt of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

A solution of 0.5 g KOH in 10 ml methanol is added to a solution of 3.05 g 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid in 30 ml acetone. The solution is evaporated to an oily residue which gives an amorphous precipitate by mixing in 40 ml ether. The precipitate is dissolved in 60 ml ethanol, the opaque solution is filtered with activated carbon and the clear filtrate is again evaporated. The oily residue is mixed with 40 ml ether and the precipitate is recovered by filtration. 2.35 g (65.3 theoret.) of potassium salt as a monohydrate (melting point 173-174 ° C) is obtained.

for C₁₇H₁₃F₂O₃K.H₂O (360.4)

30 calculated: 56.65 % C, 4.19 % H, 10.54 % F;

found: 56.71 % C, 4.04 % H, 10.39 % F.

Example 6

35 Calcium salt of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

3.05 g of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is dissolved in 55 ml 5N NaOH at 40 ° C, the clear solution is heated to 70 ° C and gradually, a solution of 1.1 g CaCl₂ is added. Upon cooling to 5 ° C a precipitate is formed which after 2 hours of standing at this temperature is removed and washed on a filter with distilled water until a negative reaction for chloride ions is obtained. The precipitate is then resuspended in 50 ml distilled water, pH is adjusted to 8 with 1N HCl under constant stirring mixed for another 30 minutes and the precipitate is removed. Upon drying to a constant weight 2.7 g (83.6 % theoret.) of calcium salt of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid (melting point 155-157 ° C) is obtained.

45 for C₃₄H₂₆F₄O₆Ca (646.7)

calculated: 6.18 % Ca;

found: 6.42 Ca.

Example 7

50

L-lysine salt of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid

4.0 g of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid is dissolved in 70 ml acetone at 40 ° C under constant stirring. After cooling to 20 ° C a solution of 2.15 g L-lysine in 10 ml H₂O is added to the clear solution. The mixture is cooled to 5 ° C and after stirring for 2 hours at this temperature the precipitate found is removed and washed in 10 ml cooled acetone. Upon drying to a constant weight 3.5 g (59.1 % theoret.) of the product (melting point 173-175 ° C) is obtained.

for C₂₃H₂₈N₂F₂O₅ (450.5)

calculated: 61.32 % C, 6.26 % H, 6.22 % N, 8.43 % F;
found: 61.13 % C, 6.43 % H, 6.01 % N, 8.26 % F.

Table I Pharmacological evaluation of acute toxicity^a anti-inflammatory effect^b in the suppression of carragenine oedema (CE) and in the inhibition of adjuvant oedema (PA) and analgesic action

Substance No.	Formula I (II) X (B')	mortality %	CE ^c inhibition %	FA ^d inhibition %	Pain ^e inhibition %
VUFB 18391	C ₂ H ₅ O	0	49	55	38
VUFB 18392	C ₂ H ₅ OCOCH ₂ NH	0	40	51	41
VUFB 18398	n-C ₄ H ₉ NH	0	33	44	33
VUFB 17629	(o-C ₆ H ₁₁ NH ₃ ⁺)	0	47	53	58
VUFB 18404	(Na ⁺)	30	44	51	35
VUFB 18405	(K ⁺)	20	39	50	47
Flobufen	OH	50	46	65	79

^a Acute oral toxicity of each substance was evaluated after a single dose of 500 mg/kg in male mice. The mortality in % is for day 7 after application;

^b Anti-inflammatory and analgesic activity was evaluated in comparison with flobufen in equimolar doses, while flobufen was administered in a dose of 20 mg/kg in the evaluation of anti-inflammatory activity and in a dose of 100 mg/kg in the evaluation of analgesic activity; the substances were administered orally as a suspension in a 0.5 % solution of methylcellulose and the oedema was measured 1 hour upon application;

Table I (continued)

- ° Suppression of the carraganine oedema was assessed according to Winter J.: Proc. Soc. Exptl. Biol. Med., 111, 544 (1962);
- ° Anti-inflammatory effect in the Freund-adjuvant test was assessed according to Horáková Z., Grimová J.: Cs. Fysiol. 17, 137 (1968);
- ° Analgesic activity was evaluated in the test of intraperitoneal irradiation with 0.7 % acid in male mice according to Wittkin L. et al.: J. Pharmacol. 133, 400 (1961);
- ° 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid.

Table II Pharmacological evaluation of acute toxicity, anti-inflammatory and analgesic activity of substance VUFB 17640 (L-lysine salt) upon oral and parenteral application

Mode of Ap- plication	Substance	Acute Toxicity ^a Dose & mortality	CE suppression ^b Dose &	FA suppression ^b Dose &	Pain suppression ^b Dose &
Oral	17640	500 0	30 46	30 58	150 77
	Flubufen ^c	500 50	20 46	20 65	100 79
Parenteral	17640	100 0	1 21	/	80 48
			10 40		

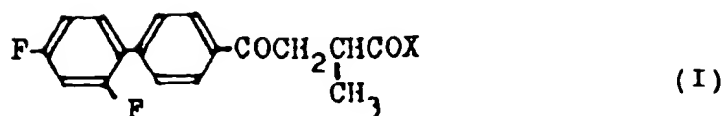
^a Acute toxicity was evaluated after a single dose of substance 17640 in male mice, namely orally as an aqueous solution, and intravenously in physiological saline solution. Mortality was followed up in groups of 10 animals for 7 days upon oral application and for 3 days upon intravenous application;

^b for oral and intramuscular application an aqueous solution of substance 17640 was used in said dose;

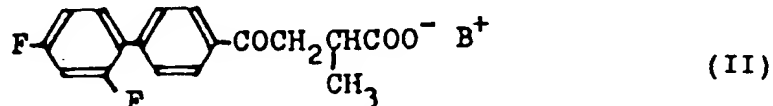
^c the standard, i.e. 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid was administered as a suspension in a 0.5 % methylcellulose solution.

Claims

- Functional derivatives of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid represented by following general formula (I)



wherein X stands for either OR in which R is an alkyl of 1 to 4 carbon atoms, or NHR in which R is an alkyl of 1 to 4 carbon atoms, or a $(\text{CH}_2)_n\text{NR}'_2$ group wherein n is 2 or 3 while R' is a methyl or an ethyl group; eventually X may represent morpholinyl; further salts of 4-(2,4-difluorobiphenyl)-2-methyl-4-oxobutanoic acid with appropriate inorganic or organic bases represented by formula (II)



wherein B^+ is either an alkaline metal cation, alkaline earth cation, cyclohexylamine cation, or lysine cation.



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EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 91109980.2
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 108, no. 5, February 1, 1988 Columbus, Ohio, USA M. KUCHAR et al. " Metabolic model and QSAR of long-acting anti-inflammatory arylaliphatic acids" page 18, abstract-no 31 304e & Pharmacochem. Libr. 1987, 10, 124-6 -----	1	C 07 C 59/88 C 07 C 69/738 C 07 C 235/34
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 C 59/00 C 07 C 69/00 C 07 C 235/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
VIENNA	06-09-1991	HOFBAUER	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			